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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/815,597	03/23/2001	Maurice J. Wolin	PP01658.002(035784/209107	7188

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EXAMINER	
SCHWADRON, RONALD B	

ART UNIT	PAPER NUMBER
1644	

MAIL DATE	DELIVERY MODE
05/04/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/815,597	WOLIN ET AL.	
	Examiner	Art Unit	
	Ron Schwadron, Ph.D.	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20-24,26-38 and 40-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20-24,26-38,40-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/9/05 has been entered.

2. Applicant's election without traverse of variant of IL-2 in the reply filed on 5/3/06 is acknowledged.

3. Applicant's election with traverse of antibody in the reply filed on 2/23/07 is acknowledged. The traversal is on the ground(s) that are stated. This is not found persuasive because of the following reasons. Regarding applicants comments it would require a serious burden to search the additional species.

The requirement is still deemed proper and is therefore made FINAL.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 20-24,26-38,40-44 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification does not provide adequate written description of the claimed invention. The legal standard for sufficiency of a patent's (or a specification's) written description is whether that description "reasonably conveys to the artisan that the inventor had possession at that time of the. . .claimed subject matter", Vas-Cath, Inc. V. Mahurkar, 19 U.S.P.Q.2d 1111 (Fed. Cir. 1991). In the instant case, the specification

does not convey to the artisan that the applicant had possession at the time of invention of the claimed inventions.

The claims encompass use of IL-2 variants. Whilst certain specific variants of IL-2 are disclosed in the specification, the claims encompass use of a vast collection of IL-2 variants that are not disclose in the specification or known in the prior art wherein the identity of such mutants is not predictable. In addition, the claims encompass use of IL-2 derived from any animal species wherein it is unclear as to what species of IL-2 other than murine or human were known in the prior art.

The skilled artisan cannot envision the detailed structure of the encompassed molecules and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. In the instant application, the nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ 2d 1601 at
1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016.

In view of the aforementioned problems regarding description of the claimed invention, the specification does not provide an adequate written description of the invention claimed herein. See The Regents of the University of California v. Eli Lilly and Company, 43 USPQ2d 1398, 1404-7 (Fed. Cir. 1997). In University of California v. Eli Lilly and Co., 39 U.S.P.Q.2d 1225 (Fed. Cir. 1995) the inventors claimed a genus of DNA species encoding insulin in different vertebrates or mammals, but had only described a single species of cDNA which encoded rat insulin. The court held that only the nucleic acids species described in the specification (i.e. nucleic acids encoding rat insulin) met the description requirement and that the inventors were not entitled to a claim encompassing a genus of nucleic acids encoding insulin from other vertebrates, mammals or humans, id. at 1240. The Federal Circuit has held that if an inventor is "unable to envision the detailed constitution of a gene so as to distinguish it from other materials. . .conception has not been achieved until reduction to practice has occurred", Amgen, Inc. v. Chugai Pharmaceutical Co, Ltd., 18 U.S.P.Q.2d 1016 (Fed. Cir. 1991). Attention is also directed to the decision of The Regents of the University of California v. Eli Lilly and Company (CAFC, July 1997) wherein is stated:

"The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 222 USPQ 369, 372-373 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. Thus, as we have previously held, a cDNA is not defined or described by the mere name "cDNA," even if accompanied by the name of the protein that it encodes, but requires a kind of specificity usually achieved by means of the recitation of the sequence of nucleotides that make up the cDNA." See Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606.

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 20-24,26-38,40-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Grillo-Lopez et al. (US Patent 6455043) in view of Halenbeck et al. (US Patent 4,931,543).

Grillo-Lopez et al. teach treatment of NHL with anti-CD20 antibodies (for example Rituximab aka IDEC C2B8) and IL-2 (see columns 13-14 and column 3, third paragraph and columns 5 and 6). Rituximab is administered clinically at a dosage of 375 mg/m2 (for example see column 9). Grillo-Lopez et al. disclose that IL-2 and antiCD20 treatment results in a synergistic effect when used to treat B cell lymphoma (see column 3, wherein NHL is a B cell lymphoma). Grillo-Lopez et al. do not disclose use of the anti-CD20 antibody and IL-2 at the particular dosages of IL-2 recited in the claims or the use of an IL-2 variant. Grillo-Lopez et al. teach that use of IL-2 at a dosage encompassed by that recited in the claims was known in the art as a treatment for NHL (see penultimate paragraph, column 14). Grillo-Lopez et al. teach treatment of NHL with antiCD20 antibody and low dose IL-2 (see column 15, third paragraph). The 3M IU/m2 dose disclosed in column 14, penultimate paragraph is the lowest clinically effective dose of IL-2 for treatment of NHL disclosed in Grillo-Lopez et al. The IL-2 variant of claim 28 was known in the art (see Example 1, Halenbeck et al.). Halenbeck et al. teach a lyophilized IL-2 pharmaceutical preparation (see column 10, penultimate paragraph).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have created the claimed invention because Grillo-Lopez et al. teach treatment of NHL with anti-CD20 antibodies and low dose IL-2 wherein Rituximab is administered clinically at a dosage of 375 mg/m2, Grillo-Lopez et al. disclose that IL-2 and antiCD20 treatment results in a synergistic effect when used to treat B cell lymphoma, Grillo-Lopez et al. teach that use of IL-2 at a dosage encompassed by that recited in the claims was known in the art as a treatment for NHL whilst IL-2 variants and the IL-2 variant of claim 28 was known in the art. One of ordinary skill in the art would have been motivated to do the aforementioned because Grillo-Lopez et al. disclose that IL-2 and antiCD20 treatment results in a synergistic effect when used to treat B cell lymphoma and Grillo-Lopez et al. teach that use of IL-2 at a dosage encompassed by that recited in the claims was known in the art as a treatment for NHL. A routineer would have determined the optimal dosage of IL-2 and antiCD20 using routine experimentation based on the low dose of IL-2 that Grillo-Lopez et al. disclose as clinically effective against NHL. A routineer would have determined the optimal schedule of administration using routine experimentation.

Regarding applicants comments, Grillo-Lopez et al. teach treatment of NHL with anti-CD20 antibodies (for example Rituximab aka IDEC C2B8) and IL-2 (see columns 13-14 and column 3, third paragraph and columns 5 and 6). Grillo-Lopez et al. teach treatment of NHL with antiCD20 antibody and low dose IL-2 (see column 15, third paragraph). The Grillo-Lopez et al. reference is considered enabled in the absence of evidence to the contrary. No such evidence has been provided by applicant. The MPEP section 2121 states:

Prior Art; General Level of Operability Required to Make a Prima Facie Case

PRIOR ART IS PRESUMED TO BE OPERABLE/ ENABLING

When the reference relied on expressly anticipates or makes obvious all of the elements of the claimed invention, the reference is presumed to be operable. Once such a reference is found, the burden is on applicant to provide facts rebutting the presumption of operability. In re Sasse, 629 F.2d 675, 207 USPQ 107 (CCPA 1980). See also MPEP § 716.07.

Thus, Grillo-Lopez et al. teach treatment of NHL with the anti-CD20 antibodies (for example Rituximab aka IDEC C2B8) and IL-2 (see columns 13-14 and column 3, third paragraph and columns 5 and 6) and treatment of NHL with antiCD20 antibody and low dose IL-2 (see column 15, third paragraph). Regarding applicants comments, Grillo-Lopez et al. disclose that IL-2 and antiCD20 treatment results in a synergistic effect when used to treat B cell lymphoma (see column 3, wherein NHL is a B cell lymphoma). Regarding applicants comments, whilst Grillo-Lopez et al. do not disclose use of the anti-CD20 antibody and IL-2 at the particular dosages of IL-2 recited in the claims, Grillo-Lopez et al. teach that use of IL-2 at a dosage encompassed by that recited in the claims was known in the art as a treatment for NHL (see penultimate paragraph, column 14) and treatment of NHL with antiCD20 antibody and low dose IL-2 (see column 15, third paragraph). The 3M IU/m2 dose disclosed in column 14, penultimate paragraph is the lowest clinically effective dose of IL-2 for treatment of NHL disclosed in Grillo-Lopez et al. and Grillo-Lopez et al. teach treatment of NHL with antiCD20 antibody and low dose IL-2 (see column 15, third paragraph).

Regarding motivation to create the claimed invention, Grillo-Lopez et al. disclose that IL-2 and antiCD20 treatment results in a synergistic effect when used to treat B cell lymphoma (see column 3, wherein NHL is a B cell lymphoma).
Regarding applicants comments, the disclosure of Grillo-Lopez et al. does not require the disclosure of clinical studies in order to provide enablement for said disclosure.
Regarding applicants comments about Gluckman et al. and Hurst et al., none of the data referred to in Gluckman et al. or Hurst et al. is disclosed in the specification and said publications were filed after the filing date of the instant application. Said references do not reflect the teachings of the specification because they represent data that is not disclosed in then specification. Said references also reflect specific use of specific reagents wherein the particular protocols disclosed in said references are not disclosed in the specification (for example use of specific patient populations in the treatment groups). The only experiment actually disclosed in the specification uses a dosage of IL-2 at 4.5 MIU/m2 and IDEC-C2B at its art recognized concentration for treating NHL (375 mg/m2, see page 28, last paragraph). Thus, the only disclosed experiments in the specification use a dosage of antiCD20 antibody that was already known in the art for treating NHL. The dosage of IL-2 used was close to the dosage disclosed in Grillo-Lopez et al. for treatment of NHL wherein there is no evidence of record that said dosage provides any result different from that used in the specification.

Regarding applicants comments about the Grillo-Lopez et al. reference, Grillo-Lopez et al. disclose that IL-2 and antiCD20 treatment results in a synergistic effect when used to treat B cell lymphoma (see column 3, wherein NHL is a B cell lymphoma). This disclosure is enabled in the absence of evidence to the contrary. Applicants comments regarding the Grillo-Lopez et al. reference fail to point out why the aforementioned disclosure lacks enablement. As applicant is well aware, clinical evidence is not required for an enabling disclosure. Therefore applicants arguments regarding the clinical trials of Grillo-Lopez et al. is irrelevant. Applicants comments regarding the claims of the Grillo-Lopez et al. patent are also irrelevant. Grillo-Lopez et al. disclose that IL-2 and antiCD20 treatment results in a synergistic effect when used to treat B cell lymphoma (see column 3, wherein NHL is a B cell lymphoma). This disclosure is enabled in the absence of evidence to the contrary. Applicants comments

regarding the Grillo-Lopez et al. reference fail to point out why the aforementioned disclosure lacks enablement.

8. Claims 20-24,26-38,40-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Grillo-Lopez et al. (WO 00/09160) in view of Halenbeck et al. (US Patent 4,931,543).

Grillo-Lopez et al. teach treatment of NHL with anti-CD20 antibodies (for example Rituximab aka IDEC C2B8) and IL-2 (see claims 12-16, page 5, first paragraph, page 6, second paragraph). Rituximab is administered clinically at a dosage of 375 mg/m2 (for example see page 16). Grillo-Lopez et al. disclose that IL-2 and antiCD20 treatment results in a synergistic effect when used to treat B cell lymphoma (see page 5, first paragraph, wherein NHL is a B cell lymphoma). Grillo-Lopez et al. do not disclose use of the anti-CD20 antibody and IL-2 at the particular dosages of IL-2 recited in the claims or the use of an IL-2 variant. Grillo-Lopez et al. teach that use of IL-2 at a dosage encompassed by that recited in the claims was known in the art as a treatment for NHL (see page 27, first paragraph). Grillo-Lopez et al. teach treatment of NHL with antiCD20 antibody and low dose IL-2 (see page 28, first paragraph). The 3M IU/m2 dose disclosed in page 27, first paragraph is the lowest clinically effective dose of IL-2 for treatment of NHL disclosed in Grillo-Lopez et al. The IL-2 variant of claim 28 was known in the art (see Example 1, Halenbeck et al.). Halenbeck et al. teach a lyophilized IL-2 pharmaceutical preparation (see column 10, penultimate paragraph).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have created the claimed invention because Grillo-Lopez et al. teach treatment of NHL the anti-CD20 antibodies and low dose IL-2 wherein Rituximab is administered clinically at a dosage of 375 mg/m2, Grillo-Lopez et al. disclose that IL-2 and antiCD20 treatment results in a synergistic effect when used to treat B cell lymphoma, Grillo-Lopez et al. teach that use of IL-2 at a dosage encompassed by that recited in the claims was known in the art as a treatment for NHL whilst IL-2 variants and the IL-2 variant of claim 28 was known in the art. One of ordinary skill in the art would have been motivated to do the aforementioned because Grillo-Lopez et al. disclose that IL-2 and antiCD20 treatment results in a synergistic effect when used to treat B cell lymphoma and Grillo-Lopez et al. teach that use of IL-2 at a dosage encompassed by that recited in the claims was known in the art as a

treatment for NHL. A routineer would have determined the optimal dosage of IL-2 and antiCD20 using routine experimentation based on the low dose of IL-2 that Grillo-Lopez et al. disclose as clinically effective against NHL. A routineer would have determined the optimal schedule of administration using routine experimentation.

Applicants arguments are as per addressed above.

9. No claim is allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ron Schwadron, Ph.D. whose telephone number is 571 272-0851. The examiner can normally be reached on Monday-Thursday 7:30-6:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571 272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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